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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/723,722	ANDERSON ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 1899*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15,18,22-25,29-31,33,34,36 and 132-134* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15,18,22-25,29-31,36 and 132-134* is/are rejected.

7)☒ Claim(s) *33 and 34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03.18.05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Amendment and Information Disclosure Statement filed March 18 are acknowledged. Claims 1-14, 16-17, 19-21, 26-28, 32, 35, and 37-131 have been cancelled in this and previous amendments. Claim 134 has been added. Claims 1, 15, 18, 33 and 34 have been amended. Claims 1, 15, 18, 22-25, 29-31, 33-34, 36, and 132-134 are pending and are the subject of this Office Action.

Detailed Action

1. Rejections

1.1. 35 USC section 112, second paragraph

Rejection of claim 32 made in the Office action of December 23, 2004 is moot because the claim has been canceled.

Claims 15, 18, 33 and 34 were rejected in the Office action of December 23, 2004 for various reasons. The rejections are now withdrawn, because the claims have been amended.

1.2. 35 USC section 112, first paragraph

1.2.1. Lack of written description

Rejection of claims 2-4, 32 and 35, made in the Office action of December 23, 2004 is moot because the claim has been canceled.

Rejection of claim 1, 22, 23, 24, 29-31, 33-34, 36, and 132-133 made in the Office action of December 23, 2004 is withdrawn, because the claims have been amended.

1.2.2. Scope of enablement

Rejection of claims 2-4, 32 and 35, made in the Office action of December 23, 2004 is moot because the claim has been canceled.

Rejection of claim 1, 22, 23, 24, 29-31, 33-34, 36, and 132-133 made in the Office action of December 23, 2004 is withdrawn, because the claims have been amended.

1.3. 35 USC section 102

Claim 1, 15, 22, 132-133 were rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,420,534, issued to Gurney et al., with priority to the provisional application 60/101,594 filed Sept. 24, 1998. This rejection is now withdrawn, because the claims have been amended.

1.4. 35 USC section 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the

subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The amended claims 1, 15, 18 and dependent claims 22 and 132-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,420,534, issued to Gurney et al., with priority to the provisional application 60/101,594 filed Sept. 24, 1998, in view of the common knowledge in molecular biology and in the field of aspartyl proteases as exemplified by the review article by Tang J. et al. (Evolution in Structure and Function of Aspartyl Proteases, Journal of Cellular Biochemistry, 1987, 33, 53-63).

The claims are directed to a protein, having beta-secretase activity **comprising** amino acid residues 63 to 452 or 46 to 452-501 or 58 to 452-501 or 46 to 419 of SEQ ID NO:2, wherein said protein

1) does not comprise amino acids 1-45 of SEQ ID NO: 2 and is purified to apparent homogeneity, or
2) is purified to run as a single in SDS PAGE gel or to be a substrate for N-terminal amino acid determination, or
3) is produced in a host cell.

The provisional application 60/101,594, which is a valid priority documents for the

Patent 6,420,534, teaches the protein human beta-secretase or gamma secretase (see the title) of 501 amino acids set forth by **SEQ ID NO: 6 (renamed SEQ ID NO: 4 in the patent), which is identical to SEQ ID NO: 2** of the instant application. Gurney et al. do not disclose SEQ ID NO: 6 as a beta-secretase, however, this is presumed to be an inherent property of the protein since the prior art and SEQ ID NO: 2 are deemed to be the same, absent a showing to the contrary.

The provisional application 60/101,594 instructs on page 9, second paragraph, and page 10, second paragraph, **how to purify** the SEQ ID NO: 6 protein to what one skilled in the art recognizes as "apparent homogeneity", which results in one band in SDS PAGE.

The provisional application 60/101,594 instructs on page 9, third paragraph through page 10 line 9 **how to efficiently express** SEQ ID NO: 6 in a host cell. Detailed instructions regarding expression vectors and host cells are presented on pages 10-11.

Gurney et al. in their provisional application **do not teach SEQ ID NO: 6 without amino acids 1-45**, although on page 5, line 6, they indicate that aspartyl proteases occur as proenzymes whose N-terminus must be cleaved for activation.

Tung et al. (Evolution in the Structure and Function of Aspartic Proteases, Journal of Cellular Biochemistry, 33, 53-63 (1987) teach, Fig. 1, that an **N-terminal pro segment of about 45-residues is cleaved off to produce mature enzymes**.

It would have been obvious to one having ordinary skill in the art at the time of invention to have the beta secretase of SEQ ID NO:6 as taught by Gurney et al. and

modify it by deleting residues 1-45 which are not necessary for the enzymatic activity of the protein. Such protein reads on structural and functional limitations of the rejected claims.

The motivation that is obvious to one having ordinary skill in the art is to have an aspartyl protease protein related to Alzheimer diseases with a potential clinical application. Alzheimer disease is caused by deposition of so called Abeta polypeptide in patient's brain. Gurney et al. provide the motivation because they have shown in the provisional application that formation of Abeta polypeptide is inhibited in cells transformed with antisense oligonucletides from cDNA encoding SEQ ID NO: 6.

The probability of success in obtaining SEQ ID NO: 6 without amino acids 1-45 is 100%, because truncation of any number of amino acid residues of a protein is a routine in the art.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was, as a whole, *prima facie* obvious.

Claims 23-25, 29-34 and are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,420,534, issued to Gurney et al., with priority to the provisional application 60/101,594 filed Sept. 24, 1998, common knowledge in molecular biology and the field of aspartyl proteases as exemplified by the review article by Tang J. et al. (Evolution in Structure and Function of Aspartyl Proteases, Journal of Cellular Biochemistry, 1987, 33, 53-63) and further in the view of the article by Viswandhan V. et al. (An Approach to Rapid Estimation of Relative Binding Affinities of

Enzyme Inhibitors: Application to Peptidomimetics Inhibitors of the Human immunodeficiency Virus Type 1 protease, J. Med. Chem. 1996, 39, 705-712).

Claims 23-25 and 29-31 are directed to a crystalline protein composition of a protein having a beta secretase activity,

(1) purified to apparent homogeneity, wherein the protein

(2) comprises amino acid residues 63 to 452 or 46 to 452-501 or 58 to 452-501 or 46 to 419 of SEQ ID NO: 2, but does not comprise amino acids 1-45 of SEQ ID NO: 2,

(2) is non-glycosylated or glycosylated, and wherein

(3) the crystalline composition comprises a beta secretase inhibitor or a substrate.

A stated above Guerney et al. teach how to purify the protein to apparent homogeneity. Gurney at al. teach also that nonglycosylated form of protein is produced in prokaryotic host cells and glycosylated in eukaryotic host cells; see page 8, the last paragraph. As explained above, an active aspartyl protease without amino acid residues 1-45 is obvious in the light of teaching by Tung et al.

Neither Gurney or Tung teach a crystalline composition consisting of crystallized polypeptide comprising amino acid residues as in (2) above or the composition that includes a beta-secretase substrate or inhibitor molecule.

Viswandhan V. et al. disclose a method of rapid estimation of binding affinities of enzyme inhibitors based on crystal structure of enzyme inhibitor complexes of a protease; see the abstract.

It would have been obvious to one having ordinary skill in the art at the time of invention to have beta secretase taught by Gurney et al. modify it as taught by Tang, et al. and crystallize it for study of interaction with substrate or inhibitorwith intention to make a drug inhibiting the beta-secretase; see above. The motivation is provided by Viswanadhan et al. because the information of interaction between an inhibitor and the enzyme "form the basis for rapid, preliminary screening of proposed derivatives of an inhibitor prior to synthesis and testing or more rigorious theoretical analysis", page 705, right column the sentence above subtitle "Computational Methodology". The motivation was already indicated in the previous Office Action of Dec. 23, 2004, "obvious to one having ordinary skill in the art is to have the composition that enables crystallographic studies of interaction between the enzyme and its inhibitor with the purpose of improving the inhibitor properties", page 11 last paragraph of the Office action. The structure-based strategies for drug design and discovery have been known for many years; see for example a review by Kuntz I. Science, 1992, 257, 1078-1082 quoted in the examiner's references. Furthermore, as explained in the Office Action of Dec. 23, 2004, the motivation to crystallize any enzyme, including claimed beta-secretase, stems from the fact of longer shelf-life of crystal form of protein than a dissolved one, with any intended use in mind; see page 12, line 9.

The probability of success in obtaining the claimed invention is 100%, because the method of protein protease crystallization is taught by Viswanadhan, and in general, the methods of crystallization have been routinely used in the art for many years now.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was, as a whole, *prima facie* obvious.

Claims 33-34 are objected as depending on rejected claim 31.

Applicants traverse the rejection made in the previous Office action emphasizing, "The present disclosure provides specific disclosure for purification to apparent homogeneity of the claimed protein not found in the '524 patent or in common general knowledge", page 14, second paragraph. Applicant's argument has been fully considered but is found not persuasive. Firstly, Applicants do not claim a method for purification the polypeptide. Applicants claim the polypeptide. Secondly, there is no proof presented by Applicants in the disclosure, that their "apparent homogeneity" is in any respect different than the one which can be reached by the methods taught by Gurney et al., as presented above. Patentability of a product is dependent on the characteristics of the product itself not on its method of making. There is no evidence on the record to show that the methods taught by Gurney et al. do not produce a product that meets the claimed limitation. Since the Office does not have the facilities for examining and comparing Applicants' protein with the protein of the prior art, the burden is on Applicants to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

1.5. Double patenting rejection

Rejection of claims 2-4 and 32 made in the Office action of December 23, 2004 and in earlier Office actions is moot because the claims have been canceled.

All provisional obviousness-type double patenting rejections of claims 1, 15, 18, 22-25, 29-31, 34 and 36 in the Office action of December 23, 2004 and in the earlier Office actions are withdrawn because the Applicants' arguments are found persuasive.

The non-provisional obviousness-type double patenting rejections of claim 1 and over claims 1, 2, and 6 of US Patent No. 5,744,346, made in the Final Office Action of Feb. 20, 2004 are maintained, because Applicants did not file a the terminal disclaimer.

Traversing this rejection Applicants argue, "To establish a *prima facie* case the Examiner must provide reasons that obtaining apparent homogeneity from an isolated preparation of lesser purity would have been obvious", p. 15, line 6.

Applicants argument is fully considered but found not pertinent and therefore persuasive. Patentability of a product is dependent on the characteristics of the product itself and not on its method of making. Both products, the one of claim 1 of the instant application and that of claims in the patent possess the same enzymatic characteristics and source of origin independently of the method of their purification. Although the method of purification in the patent and in the instant application are different, these are the products that are claimed and not the methods.

2. Conclusion

Claims 1,15,18, 22-25, 29-31, 36 and 132-134 are rejected. Claims 33 and 34 are objected. Limiting the scope of the claims to polypeptides consisting of truncated forms of beta secretase would place the claims in allowable conditions.

Applicants attention is turned to the document WO00/58479, published 23 March 2000, with valid priority to March 26, 1999, which is relevant to the instant application.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-

0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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